REMARKS

This is in response to the Office Action of August 8, 2008. The specification is amended to delete unnecessary hyperlink citations. Claims 1-7 are pending in the application. Claim 1 is amended to clarify that the macrolide compound 11107B represented by formula (I) is provided ***before*** conducting the recited process steps (A) to (C). Claim 5 is amended to depict formulas (I) and (II) recited therein. No new matter is introduced by this Amendment.

Interview

Applicants gratefully acknowledge an interview between Examiner Shahnan Shah and their representative, Richard Gallagher, on November 10, 2008. During the interview, significant differences between bioconversion and fermentation were discussed. Specifically, it was pointed out that bioconversion is the transformation of one complex organic compound into another complex organic compound by an enzyme or a living organism, while fermentation is the splitting of a complex organic compound into simpler substances. The present invention involves bioconversion, not fermentation. The Examiner indicated that she would take these differences into account when she reconsiders the present application.

Objection to the Specification

The outstanding Office Action objected to the specification as improperly citing a website. The Examiner states that an "attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference." The citations in question merely indicated where certain information was obtained at pages 9, 10, and 22 of the specification. The specification at these pages recited that "The DNA sequences of known strains were obtained from Japan DNA Data Bank (www.ddbj.nig.ac.jp/) to examine the homology of 400 to 500 bases on the 5' terminal side of the 16s rRNA genes." The recited reference to the website was therefore not necessary to comply with 35 U.S.C. § 112, and it has accordingly been deleted. Reconsideration and withdrawal of the objection to the specification are respectfully requested.

Rejection under 35 U.S.C. § 102(b)

Claims 1, 3, and 5 were rejected under 35 U.S.C. § 102(b) as being anticipated by Mizui et al., WO 02/0600890-A1 (hereinafter, "Mizui et al."). Office Action, pages 5-6. The US equivalent specification – U.S. Patent Application Publication No. 2006/0079572, U.S. Patent Application Serial No. 11/213,962 – is a divisional application of U.S. Patent Application Serial No. 10/470,806 (issued as U.S. Patent No. 7,026,352). All references to Mizui et al., below, refer to the U.S. publication equivalent of Mizui et al. The rejection is respectfully traversed.

The Examiner contends that Mizui et al. disclose conversion of macrolide 11107B to 11107D using a biological transformation method. The Examiner presumes that the strain of bacteria used in Mizui et al. may be FERM BP-8551, "since the required bioconversion is achieved by the strain of [Mizui] et al."

The abstract of Mizui et al. disclose fermentative production of a 12-membered ring macrolide using *Streptomyces* sp. Mer. 11107. The compound formula disclosed in the abstract of Mizui et al. appears to encompass compound 11107B and the bacterial species disclosed is encompassed by part (A) of present claim 1. The compound at paragraphs [0016] to [0017] (formula 2) of Mizui et al. is the claimed 11107B where R^7 is acetoxy and R^{21} is hydroxy.

Presently claimed compound 11107B is disclosed at paragraph [0415], Example A4. Presently claimed compound 11107D is disclosed at paragraph [0434], Example A6. Claim 24 of Mizui et al. discloses culturing to obtain the starting materials, from which various modifications may be made.

However, Mizui et al. fails to disclose a method of producing macrolide 11107D by incubating a bacterial strain belonging to the genus Mortierella, the genus Streptomyces or the family Micromonosporaceae with the macrolide of 11107B. (*See*, Mizui et al., at paragraph [0274]). That is – while Mizui et al. may disclose 11107B and 11107D – Mizui et al. do not disclose ***how to synthesize 11107D from 11107B using a bacteria***, as required by Applicants' claims.

SUMMARY. The Mizui et al. reference shows obtaining 11107B and 11107D biologically from a starting nutrient medium. The reference fails to show 11107B used as a starting material and also fails to show 11107B being hydroxylated at the 16-position by means

of a microorganism. Mizui et al. fails to show definitively a strain of Mer-11107 bioconverting from 11107B to 11107D by hydroxylation at the 16-position. In other words, Mizui et al shows

nutrient medium → 11107B, 11107D

while the present invention, in contrast, requires

11107B → 11107D.

Withdrawal of the rejection of claims 1, 3, and 5 under 35 U.S.C. § 102(b) as being anticipated by Mizui et al. is in order and is earnestly solicited.

Rejection under the Obviousness-Type Double Patenting Doctrine

Claims 1, 3, and 5 were provisionally rejected on the ground of obviousness-type double patenting, over claims 1 and 24 of co-pending application Serial No. 11/213,962. Office Action, pages 3-5. The rejection is respectfully traversed.

The invention disclosed in claims 1 and 24 of application Serial No. 11/213,962 requires a fermentation step to obtain 11107B or 11107D. However, the reference application fails to disclose or suggest hydroxylation (-OH) of the fermentation product at the 16-position. The presently claimed invention includes production of a macrolide compound 11107D of formula (II) having a hydroxyl (OH) group at the 16-position, starting from a macrolide compound 11107B of formula (I) which has no hydroxyl (OH) group at the 16-position. The presently claimed production is performed by incubation with a microorganism.

Claims 1 and 24 of the reference application fail to show 11107B used as a starting material and also fails to show 11107B being hydroxylated at the 16-position by means of a microorganism. Accordingly, withdrawal of the double patenting rejection is in order and is earnestly solicited.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 3 and 5 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Seki-Asano et al., *J. Antibiotics*, 47(12):1395-1401, 1994 (hereinafter, "Seki-Asano et al.). Office Action, pages 6-7. The rejection is respectfully traversed.

The Examiner states that Seki-Asano et al. disclose isolation and characterization of a new 12-membered macrolide FD-895 produced by biological transformation by *Streptomyces hygroscoicus* A-9561. However, Seki-Asano et al. do not disclose incubating macrolide 11107B with the claimed bacterial strains to produce the macrolide of 11107D. Seki-Asano et al. merely disclose isolation of a macrolide, which is different in structure from the claimed 11107D macrolide, from the spent media of a culture of *Streptomyces hygroscoicus* A-9561.

Furthermore, the Examiner fails to appreciate all of the structural differences between the FD-895 structure of Seki-Asano et al. and the presently claimed structure of 11107D. The Examiner states that it is obvious to substitute a hydroxyl group for a methyl group in this family of antibiotics. However, this is not the only difference between the structures. For instance, 11107D has a hydroxyl at position 21, not a methoxy group. Further, 11107D has no hydroxyl at position 17. Additionally, 11107D has a hydroxyl at position 16, not a methyl group, as pointed out by the Examiner. These changes are not merely a substitution of a methyl group for a hydroxyl. Seki-Asano et al. provide no rationale for making all of these changes.

SUMMARY. Seki-Asano's FD-895 is significantly different from Applicants' 11107B and 11107D, having a hydroxyl group in the 17-position and having a methoxy group in the 21-position. FD-895 differs from 11107B in having no hydroxyl group at the 16-position. FD-895 is obtained directly from a medium of *Streptomyces hygroscoicus* A-9561. See Seki-Asano, page 1395, lines 11-12 from the bottom. The Seki-Asano reference provides no teaching relevant to biological hydroxylation of a particular compound at a particular position. No motivation to or rationale for hydroxylation of 11107B at position 16 is provided by the Seki-Asano reference in particular or by the prior art in general. The Seki-Asano reference fails to show 11107B used as a starting material and also fails to show a microorganism being used to hydroxylate a particular compound at a particular position (much less, 11107B at the 16-position) and also fails to show 11107D being obtained as a final product. Seki-Asano fails to suggest that *Streptomyces hygroscoicus* A-9561 can be used to bioconvert 11107B to 11107D by hydroxylation at the 16-position.

Withdrawal of the rejection of claims 1, 3, and 5 under 35 U.S.C. § 103(a) as being unpatentable over Seki-Asano et al. is in order and is earnestly solicited.

CONCLUSION

If the Examiner has any questions or comments, please contact Richard Gallagher, Registration No. 28,781, at the offices of Birch, Stewart, Kolasch & Birch, LLP. Mr. Gallagher can be reached at (703) 205-8008.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____

RF

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